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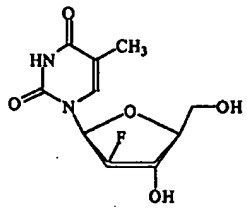

(1)

(57) Abstract

The present invention relates to a novel and improved process for preparing 2'–fluoro–5–methyl–β–L–arabinofuranosyluridine represented by formula (1) which shows anti–viral activity, especially potent anti–viral activity against hepatitis B–virus and Epstein–Barr virus.

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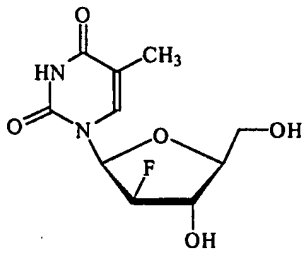
PROCESS FOR PREPARATION OF 2'-FLUORO-5-METHYL-β-L-ARABINO-FURANOSYLURIDINE

TECHNICAL FIELD

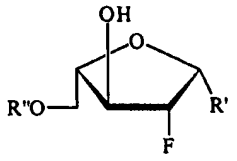
The present invention relates to an improved process for preparing 2'-fluoro-5-methyl-β-L-arabinofuranosyluridine(generic name: Levovir, hereinafter referred to as "L-FMAU") represented by formula (1), which shows anti-viral activity, especially potent anti-viral activity against hepatitis B-virus(HBV) and Epstein-Bar virus(EBV):



(1)

BACKGROUND ART

Various nucleoside compounds, including L-FMAU of formula (1) have been disclosed (see, for example, International Publication No. WO 95/20595):



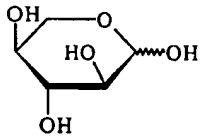
(2)

in which

R' represents purine or pyrimidine base; and
R" represents hydrogen, acyl, alkyl, monophosphate, diphosphate or triphosphate.

Nucleoside compounds of formula (2) exhibit anti-viral activity against HBV and EBV. Among these nucleoside compounds, L-FMAU shows particularly potent anti-viral activity against HBV and EBV with very low cytotoxicity and is, therefore, preferred as an anti-viral agent. Nucleoside compounds of formula (2), including L-FMAU, are useful in the prevention and treatment of HBV infections and related conditions, such as anti-HBV antibody positive and HBV-positive conditions, chronic liver inflammation caused by HBV, cirrhosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue. In addition, they can also be used for the treatment of EBV-associated disorders.

According to the method disclosed in International Publication No. WO 95/20595, L-FMAU of formula (1) may be prepared using L-xylose of formula (3) as a starting material :



(3)

L-xylose of formula (3) cannot be obtained from natural substances and must therefore be produced by synthetic methods. When L-xylose is used as the starting material, the production cost of L-FMAU is therefore very high.

OBJECT OF INVENTION

It has been discovered that L-FMAU can be economically prepared from L-arabinose, which is present in many natural substances and, thus, is an inexpensive starting material, thereby completing the present invention.

SUMMARY OF THE INVENTION

An improved process for preparing L-FMAU is provided which used L-arabinose as the starting material.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a schematic diagram of one method for the production of L-FMAU according to the disclosed process.

BRIEF DESCRIPTION OF THE INVENTION

The term alkyl, as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbon of C_1 to C_{10} and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The alkyl group can be optionally substituted with one or more moieties selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., "Protective Groups in Organic Synthesis," John Whiley and Sons, Second Edition, 1991. The term lower alkyl, as used herein, and unless otherwise specified, refers to a C_1 to C_4 saturated straight or branched alkyl group.

The term aryl, as used herein, and unless otherwise specified, refers to phenyl, biphenyl, or naphtyl, and preferably phenyl. The aryl group can be optionally substituted with one or more moieties selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991.

The term aralkyl or arylalkyl refers to an aryl group with an alkyl substituent.

The term acyl refers to moiety of the formula $-C(O)R^1$, wherein R^1 is alkyl; alkyoxyalkyl including methoxymethyl; arylalkyl including benzyl; aryloxyalkyl such as phenoxymethyl; aryl including phenyl optionally substituted with halogen, C_1 to C_4 alkyl or C_1 to C_4 alkoxy.

According to the present invention, the desired compound, L-FMAU, of formula (1) can be economically prepared from the starting material of formula (4) by a process that utilizes the reaction set out in Figure 1, wherein:

a) the starting material, L-arabinose of formula (4), is reacted with a compound of formula (18) to obtain a compound of formula (5);

b) the compound of formula (5) is condensed with a compound of formula (19) to obtain the compound of formula (6), which is oxidized to obtain the compound of formula (7), which is then reduced to obtain the compound of formula (8);

c) the compound of formula (8) is treated with an acid to obtain the compound of formula (9), which is treated with the compound of formula (18) in the presence of an acid to obtain the compound of formula (10), which is reacted with an acyl-chloride such as benzoyl chloride to obtain the compound of formula (11), which is then reacted with an acid, for example, acetic acid and acetic anhydride in the presence of sulfuric acid to obtain the compound of formula (12);

d) the compound of formula (12) is converted into the compound of formula (13);

e) the compound of formula (13) is reacted with an agent for introducing a reactive leaving group to obtain the compound of formula (14);

f) the compound of formula (14) is fluorinated to obtain the compound of formula (15), which is subjected to halogenation to obtain the compound of formula (16), which is then condensed with a thymine base to obtain the compound of formula (17); and

g) the compound of formula (17) is treated with ammonia in methanol to produce the desired L-FMAU of formula (1).

In the above reaction scheme, R represents a hydroxy-protecting group such as alkyl, aryl, halogenoalkyl, aralkyl, etc., R_1 and R_2 independently of one another represent hydrogen, alkyl or aryl, L represents a reactive leaving group such as imidazolylsulfonyl, toluenesulfonyl, methanesulfonyl, trifluoromethanesulfonyl, etc., and Hal

represents a halogen atom such as chloro or bromo.

The process of the present invention is explained in more detail below.

As illustrated in Figure 1, by reacting the starting material, L-arabinose of formula (4), with an alcohol of formula (18), for example, benzyl alcohol, in the presence of hydrogen chloride gas, the 1-hydroxy group of L-arabinose is protected to produce the compound of formula (5).

In reaction b), the compound of formula (5) prepared in the reaction a) is condensed with a propane derivative of formula (19), for example, 2,2-dimethoxypropane, to produce the compound of formula (6). The compound of formula (6) is oxidized to produce the compound of formula (7), which is subsequently reduced to produce the compound of formula (8). In this reaction, oxidizing agents which can preferably be used include aqueous chromic acid (CrO_3), sodium dichromate (Na_2CrO_7), pyridinium chlorochromate (POC), pyridinium dichromate (PDC), potassium permanganate ($KMnO_4$), lead tetraacetate/pyridine, oxygen over platinum/carbon catalyst, RuO_4, $RuO_4/NaIO_4$, dimethylsulfoxide/dicyclohexylcarbodiimide (DMSO/DCC) and a proton donor, silver carbonate, triphenyl bismuth carbonate, Oppenauer oxidation (aluminum alkoxides in acetone), chlorine dioxide (ClO_2), dimethylsulfoxide/oxalyl chloride (DMSO/$(COCl)_2$), dimethylsulfoxide/sulfuryl chloride (DMSO/SO_2Cl_2), dimethylsulfoxide/thionyl chloride (DMSO/$SOCl_2$), dimethylsulfoxide/toluenesulfonyl chloride (DMSO/TsCl), dimethylsulfoxide/trifluoroacetic anhydride (DMSO/$(CF_3CO)_2O$), dimethylsulfoxide/acetic anhydride (DMSO/Ac_2O), etc. Among them, pyridinium dichromate in the presence of a solvent such as dichloromethane is particularly preferred. Reducing agents which can preferably be used include sodium borohydride ($NaBH_4$), diisobutylaluminum hydride (DIBAL-H), lithium borohydride ($LiBH_4$), sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), lithium aluminum hydride ($LiAlH_4$), potassium borohydride (KBH_4), Raney nickel, rhodium/hydrogen (H_2), palladium/hydrogen, platinum/hydrogen, rubidium/hydrogen,

rubidium-silica/hydrogen, etc. Among them, sodium borohydride ($NaBH_4$) is particularly preferred.

In reaction c), the compound of formula (8) is treated with an acid such as trifluoroacetic acid to remove the hydroxy-protecting group of the compound(8) and thereby produce the compound of formula (9), which is then treated with the compound of formula (18) in the presence of an acid, for example, methanol in the presence of hydrochloric acid to produce the compound of formula (10), which has a ribofuranose structure. The compound of formula (10) is then reacted with an acylchloride such as benzoyl chloride in the presence of a base to protect all the hydroxy groups of the compound of formula (10) with benzoyl groups, thereby producing the compound of formula (11). The compound of formula (11) is then treated with an acid such as acetic acid and anhydrous acetic acid in the presence of sulfuric acid to produce the compound of formula (12). The series of reaction steps for preparing the compound of formula (12) from the compound of formula (8) can preferably be practiced consecutively, without isolation of any intermediate.

In reaction d), the compound of formula (12) produced in reaction c) is treated with hydrogen chloride in a solvent such as dichloromethane, cyclohexane, chloroform, etc., and then treated with water in a solvent such as acetonitrile to produce the compound of formula (13). In this reaction, the reaction by-product 1-hydroxy-isomer must be removed by treating with an ether such as dibutyl ether, diethyl ether, etc.

In reaction e), the compound of formula (13) is reacted with an agent for introducing a suitable reactive leaving group, for example, sulfuryl chloride and imidazole, to produce the compound of formula (14). This reaction can be carried out in the presence of a solvent such as dimethylformamide, dichloromethane, etc.

In reaction f), the compound of formula (14) produced in reaction e) is fluorinated in the presence of a solvent such as ethyl acetate,

thereby substituting the reactive leaving group with fluorine to produce the compound of formula (15). In this reaction, the preferred fluorinating agent includes potassium hydrogen fluoride (KHF_2)/hydrofluoric acid/pyridine or hydrofluoric acid/amine such as triethylamine. The resulting compound of formula (15) is then halogenated, for example, with hydrobromic acid or hydrochloric acid, in the presence of acetic acid to produce the compound of formula (16). The compound of formula (16) is then reacted with thymine base in the presence of hexamethyldisilazane and ammonium sulfate to produce the compound of formula (17). This reaction can preferably be carried out in the presence of a solvent, for example, chloroform, dichloromethane, 1,2-dichloroethane, acetonitrile, etc.

In reaction g), the compound of formula (17) produced in reaction f) is treated with ammonia in the presence of a solvent to remove the benzoyl group, the hydroxy-protecting group, from rhe compound of formula (17), thereby producing the desired compound L-FMAU.

Although various aspects of the present invention are illustrated by the following examples, the present invention is not in any manner limited by these examples. Other reactants can be used as known to those of ordinary skill, which perform substantially the same function. In the examples, the number of the compound in parentheses corresponds to the number in the reaction scheme A.

Example 1 : Preparation of 1-O-benzyl-β-L-arabinoside (5)

Benzyl alcohol 1000mℓ was saturated with hydrogen chloride for 40 minutes at 0℃, 200g(1.33 mole) of L-arabinose was added and the resulting mixture was stirred at room temperature for 10 hours, during which a quantity of the compound (5) precipitated. To induce additional precipitation, 1.5 ℓ of ethyl acetate was slowly added while the mixture was stirred. The resulting solid product was filtered, washed with ethyl acetate and then dried in air to obtain 300g (Yield : 94%) of the title compound (5) in the form of a white solid.

m.p. : 170-171℃

^{1}H NMR δ (ppm) : 3.46(q, 1H, J=2.87, 11.8), 3.63-3.73(m, 4H), 4.45(d, 1H, J=12.8), 4.76(d, 1H, J=12.32), 7.29-7.38 (m, 5H)

Example 2 : Preparation of 1-O-benzyl-3,4-O-isopropylidene-β-L-riboside (8)

A mixture of 200g(0.83 mole) of 1-O-benzyl-β-L-arabinoside (5), 240mℓ(1.95 mole) of 2,2-dimethoxypropane and 4g(0.02 mole) of p-TsOH · H_2O in 2000mℓ of acetone was stirred at room temperature for 2 hours. The reaction mixture thereby obtained was neutralized with triethylamine and evaporated under reduced pressure to obtain the compound (6) in the form of a yellowish syrup, which was used for the next reaction without further purification.

To a mixture of the compound (6) and 240g(0.63 mole) of pyridinium dichromate in 2000mℓ of dichloromethane was added 240mℓ(2.54 mole) of acetic anhydride at 0℃ and the mixture thereby obtained was then refluxed until the starting material disappeared (ca. 4 hours). At this time, the system was vented. The solvent was removed under reduced pressure until the mixture occupied one-third of its initial volume and the residue was poured into 1500mℓ of ethyl acetate with vigorous stirring accomplished using a mechanical stirrer. The mixture thus obtained was filtered through a celite pad and the filter cake was thoroughly washed with ethyl acetate. The blackish combined filtrate was filtered through a silica gel (2-20 micron) column (20cm height, 10cm diameter). The silica gel was washed with ethyl acetate until the compound (7) was no longer detected by TLC. The clear combined filtrate thereby obtained was evaporated to yield the compound (7) in the form of a syrup, which was coevaporated twice with toluene.

The purified syrup (7) thus obtained was dissolved in 2000mℓ of methanol and cooled to -20℃. 40g(1.06 mole) of $NaBH_4$ pellets were very slowly added to the resulting solution over 3 hours at -20℃. After

completion of the reaction, the solution was neutralized with acetic acid, evaporated under reduced pressure to obtain a white solid residue. The residue was partitioned between 1000㎖ of ethyl acetate and 200㎖ of water. The aqueous layer was extracted with 100㎖ of ethyl acetate. The combined organic layer was washed with 200㎖ of brine, dried over $MgSO_4$ and then evaporated to yield a white solid, which was recrystallized from 700㎖ of hot hexane to yield 123g (Yield : 53% from the compound (5)) of the compound (8) in the form of a white crystal.

m.p. : 79-80℃

$[\alpha]^{25}_D$ = +143° (c 0.7, ethanol)

^{1}H NMR δ (ppm) : 1.37(s, 3H), 1.55(s, 3H), 2.37(d, 1H, J=6.45), 3.71-3.76 (m, 2H), 3.86(q, 1H, J=3.44 and 12.89), 4.27-4.30(m, 1H), 4.49-4.52(m, 1H), 4.56(d, 1H, J=11.8), 4.83(d, 1H, J=11.8), 4.86(d, 1H, J=5.40), 7.26-7.36(m, 5H)

Example 3 : Preparation of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-L-ribofuranose (12)

201g(0.717 mole) of the compound (8) dissolved in 1000㎖ of 4% trifluoroacetic acid(CF_3COOH) was refluxed until the starting material (ca. 1 hour) and the intermediate (1-O-benzyl derivative) had disappeared (ca. 4-8 hours). The reaction mixture was cooled to room temperature and washed with dichloromethane (4×500㎖) to remove benzyl alcohol. The aqueous layer thereby obtained was evaporated in vacuo and coevaporated with toluene (2×200㎖) to yield the compound (9) in the form of a yellowish syrup, which was completely dried under high vacuum to remove a trace amount of water.

The compound (9) was dissolved in 2000㎖ of methanol and 15.8g(0.43 mole) of HCl (gas) was bubbled into the mixture at room temperature. The mixture thereby obtained was stirred at room temperature for 2 hours, neutralized with 183㎖ of pyridine and concentrated in vacuo at 30-35℃ to give a yellowish syrup, which was in turn coevaporated with pyridine to yield the compound (10) in the form

of a yellowish syrup. The compound (10) was dissolved in 800mℓ of pyridine and 212mℓ of benzoyl chloride was added dropwise to the mixture at 0℃. The mixture was stirred at room temperature for 8 hours. After the reaction had gone almost to completion, the mixture was heated at 45℃ for 1.5 hour. The mixture was cooled to room temperature and ice was added to remove the remaining benzoyl chloride. Pyridine was evaporated from the mixture at 35-40℃ until the mixture occupied half of its initial volume. The residue was dissolved in 1500mℓ of ethyl acetate, which was washed in succession with 500mℓ of cold water, 576mℓ of cold 3N H_2SO_4, 500mℓ of aqueous sodium bicarbonate (×2), and 500mℓ of brine, in that order. The organic layer was dried over $MgSO_4$ and activated carbon, filtered through a silica gel (2-20μ) pad and evaporated to obtain the compound (11) in the form of a yellowish syrup.

To a mixture of the compound (11) dissolved in 144mℓ(2.52 mole) of acetic acid and 334mℓ(3.54 mole) of acetic anhydride, 48mℓ(0.9 mole) of c-H_2SO_4 was slowly added dropwise at 0℃, during which crystallization occurred. The mixture was brought to room temperature and kept in a refrigerator overnight. The mixture was poured into 700mℓ of an ice-water mixture, filtered and the filter cake was washed twice with cold water. The solid was dissolved in 2000mℓ of ethyl acetate, which was washed in succession with 500mℓ of water, 500mℓ of saturated sodium bicarbonate and 500mℓ of brine. The organic layer was dried over $MgSO_4$ and activated carbon and the resulting mixtrue was filtered through a silica gel (2-20μ) pad. The solvent was removed and the residue was recrystallized from methanol to obtain 144.7g (Yield : 40% from the compound (8)) of the compound (12) in the form of a white solid.

m.p. : 124-125℃

$[\alpha]^{25}_D$ = -22.1° (c 1, pyridine)

^{1}H NMR($CDCl_3$) δ (ppm) : 8.90-7.32(m, 15H, Ar-H), 6.43(s, 1H, H-1), 5.91(dd, 1H, H-3, J=4), 5.79(d, 1H, H-2, J=8), 4.81-4.76(m, 2H, H-4 and H-5), 4.54-4.49(m, 1H, H-5), 2.00(s, 3H, CH_3COO)

Example 4 : Preparation of 1,3,5-tri-O-benzoyl-α-L-ribofuranose (13)

HCl (gas) was bubbled for 1.5 hours into a solution of 50g(99.16 mmole) of the compound (12) dissolved in 460mℓ of anhydrous dichloromethane and 7.5mℓ of acetyl chloride at 0℃. The resulting solution was kept in a refrigerator for 12 hours and then evaporated in vacuo. The residue was coevaporated with toluene (3×150mℓ) at 45℃ and redissolved in 105mℓ of acetonitrile. To this solution, 13mℓ of water was added dropwise at 0℃. A white solid began to precipitate from the mixture after 30 minutes, after which the mixture was kept in a refrigerator for 2 hours to induce additional precipitation. After filtration of the resulting solid, the filter cake was carefully washed with cold diethylether to remove the reaction by-product 1-hydroxy-isomer, which is indistinguishable by TLC from the compound (13). The white solid thereby obtained was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate to remove the remaining HCl, dried over $MgSO_4$ and filtered. The solvent was removed from the filtrate to obtain 29.2g (Yield : 63.7%) of the compound (13) in the form of a white solid.

m.p. : 137-139℃

$[\alpha]^{20}_D$ = -82.01° (c 1.5, $CHCl_3$)

^1H NMR($CDCl_3$) δ (ppm) : 7.31, 8.19(m, 15H, Ar-H), 6.69(d, J=4.6Hz, 1H, H-1), 5.59(dd, J=6.7, 1.8Hz, 1H, H-3), 4.64, 4.80(m, 4H, H-2, H-4 and H-5), 2.30(br s, D_2O exchangable, OH)

Example 5 : Preparation of 1,3,5-tri-O-benzoyl-2-O-imidazolyl-sulfonyl-α-L-ribofuranose (14)

107.0g(0.232 mole) of the compound (13) was dissolved in 1070mℓ of dichloromethane and 214mℓ of dimethylformamide, to which 62.5g(37.2 mℓ, 0.463 mole) of sulfuryl chloride was added dropwise at a low

temperature (-10 to -78℃). The resulting solution was stirred at room temperature for 3 hours and then cooled in an ice-bath. The solution was stirred while 157.8g(2.32 mole) of imidazole was added portionwise at the rate keeping the temperature of reaction mixture under 5℃. The resulting mixture was stirred at room temperature for 20 hours, after which 400㎖ of ice-water was added. The aqueous layer was extracted three times with 100㎖ of dichloromethane (3×100㎖). The combined organic solution was washed with 200㎖ of brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and dimethylformamide was removed under high vaccum. The syrupy residue was coevaporated with 100㎖ of 2-propanol under reduced pressure to obtain a white solid product (14), which was used for the next reaction without further purification.

Example 6 : Preparation of 1-(3,5-di-O-benzoyl-2-fluoro-β-L-arabinofuranosyl)thymine (17)

A mixture of the imidazolate (14) obtained from Example 5, 224.1g(1.39 mole) of triethylamine-3HF and 824㎖ of ethyl acetate was heated at 80℃ for 3 hours, 70.3g(92.5㎖, 0.696 mole) of triethylamine was slowly added thereto and the mixture thereby obtained was stirred for one additional hour at the same temperature, after which the mixture was cooled to room temperature. The resulting solution was poured into ice-water containing $NaHCO_3$ to neutralize it to pH 7. The aqueous layer was extracted three times with 100㎖ of ethyl acetate (3×100㎖). The combined organic solution was washed with brine and dried over Na_2SO_4. The solvent was removed and the residue was redissolved in 300㎖ of dichloromethane, filtered through a silica gel pad and washed with dichloromethane. The solvent was removed to obtain 101.0g of crude 2-fluoro-sugar product (15), which was redissolved in 150㎖ of dichloromethane. 195.9㎖(88.2g, 1.09 mole) of hydrobromic acid/acetic acid(45% w/v) was added to the solution at 0℃ and then stirred at room temperature for 15 hours. The resulting solution was evaporated to dryness under reduced pressure to give a syrup, which was coevaporated with toluene (3×100㎖) to obtan the sugar bromide (16) in the form of a

semisolid, which was then redissolved in 200mℓ of chloroform for the condensation reaction described below.

A mixture of 55.44g(0.44 mole) of thymine, 5g of ammonium sulfate($(NH_4)_2SO_4$) and 212.5g(278.9mℓ, 1.32 mole) of hexamethyldisilazane in 1900mℓ of chloroform was refluxed for 24 hours to give a nearly clear solution. A solution of sugar bromide (16) in chloroform was added and the resulting mixture was refluxed for additional 24 hours and then cooled to room temperature. 200mℓ of water was added to the reaction mixture, which was stirred at room temperature for 30 minutes and then filtered. The organic layer was separated, dried over Na_2SO_4, and filtered through a celite pad, which was then washed with ethyl acetate. The combined organic solution was evaporated to give a solid which was recrystallized from 100mℓ of ethanol to obtain 78.0g (Yield : 69.5% from the alcohol compound (13)) of 3,5-O-dibenzoyl L-FMAU (17) in the form of a crystal.

m.p. : 118-120℃

$[\alpha]^{20}_D$ = +22.40° (c 0.31, $CHCl_3$)

UV (MeOH) λ_{max} 264.0nm

^1H NMR($CDCl_3$) δ (ppm) : 8.55(s, NH), 7.37, 8.12(m, Ar), 6.35(dd, J_{F-H}= 22.4Hz, H-1'), 5.64(dd, J_{F-H}=20.4Hz, H-3'), 5.32(dd, J_{F-H}=50.2Hz, H-2'), 4.82(m, H-5), 4.50(m, H-4'), 1.76(s, CH_3)

Example 7 : Preparation of 2'-fluoro-5-methyl-β-L-arabinofuranosyluridine (1)

NH_3 gas was bubbled for 2-3 hours into a suspension of 83.0g(0.18 mole) of the compound (17) in 1000mℓ of methanol to obtain a clear solution, which was then stirred at room temperature for an additional 48 hours. The solvent was removed under reduced pressure and the residue was triturated with diethyl ether. The resulting solid was collected by filtration, redissolved in 500mℓ of methanol and twice decolorized with charcoal. Methanol was removed and the resulting solid

was refluxed with 200mℓ of acetonitrile for 2 hours. The resulting mixture was cooled in refrigerator for 15 hours and then filtered to obtain 35.6g (Yield : 77.35%) of a white solid. The mother liquor was concentrated to dryness and purified by silica gel column chromatography (1-10% methanol in chloroform) to obtain a white solid, which was refluxed with 20mℓ of acetonitrile to obtain 4.98g (Yield : 10.8%) of the second crop of the product. Total yield was raised to 88.2% (40.58g).

m.p. : 185-187℃

$[\alpha]^{20}_D$= -112.06° (c 0.23, methanol)

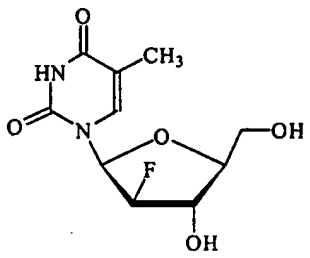
UV (H_2O) λ_{max} 265.0 (ε 9695)(pH 2), 265.5 (ε 9647)(pH 7), 265.5nm (ε 7153)(pH 11)

^{1}H NMR(DMSO-d_6) δ (ppm) : 11.45(s, NH), 7.59(s, H-6), 6.10(dd, J_{F-H}= 15.4Hz, H-1'), 5.88(d, 3'-OH), 5.12(t, 5'-OH), 5.04(dt, J_{F-H}=52.8Hz, H-2'), 4.22 (dq, J_{F-H}=18.4Hz, H-3'), 3.76(m, H-4'), 3.63(m, H-5'), 1.78(s, CH_3)

The invention has been described with reference to its preferred embodiments. Variations and modifications of the invention will be obvious to those skilled in the art from the foregoing detailed description of the invention. It is intended that all of these variations and modifications be included within the scope of the appended claims.

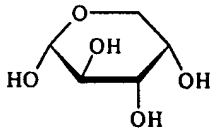
WHAT IS CLAIMED IS :

1. A process for preparing 2'-fluoro-5-methyl-β-L-arabino-furanosyluridine(L-FMAU) of formula (I),



(1)

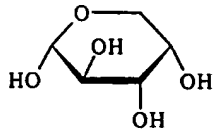
characterized by using L-arabinose of formula (4) as a starting material:



(4)

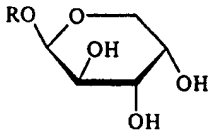
2. The process as defined in claim 1, wherein:

a) L-arabinose of formula (4) is reacted a compound of formula (18) to obtain a compound of formula (5),



(4)

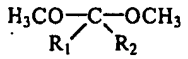
R—OH (18)



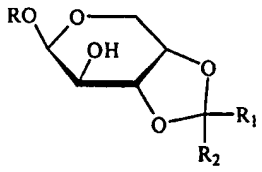
(5)

wherein R represents a hydroxy-protecting group;

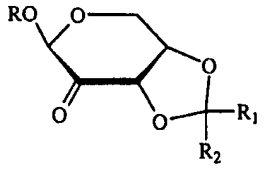
b) the compound of formula (5) is condensed with a compound of formula (19) to obtain the compound of formula (6); the compound of formula (6) is oxidized to obtain the compound of formula (7), which is then reduced to obtain the compound of formula (8),



(19)



(6)



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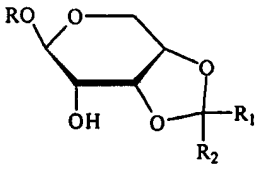
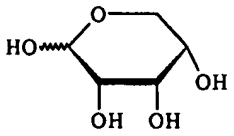


(8)

wherein R_1 and R_2 independently of one another represent hydrogen alkyl or aryl, and R represents a hydroxy-protecting group;

c) the compound of formula (8) is treated with an acid to obtain the compound of formula (9); the compound of formula (9) is treated with a compound of formula (18) in the presence of an acid to obtain the

compound of formula (10); and the compound of formula (10) is reacted with benzoyl chloride to obtain the compound of formula (11), which is then reacted with acetic acid and acetic anhydride in the presence of sulfuric acid to obtain the compound of formula (12);,



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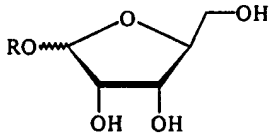

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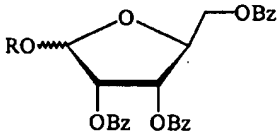
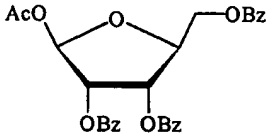


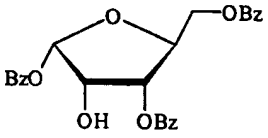
(11)



(12)

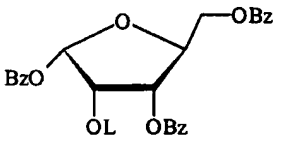
wherein R is a hydroxy-protecting group;

d) the compound of formula (12) is converted into the compound of formula (13);



(13)

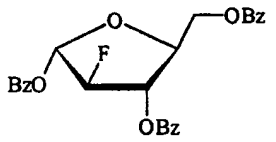
e) a reactive leaving group is introduced into the compound of formula (13) to obtain the compound of formula (14),



(14)

wherein L represents a reactive leaving group;

f) the compound of formula (14) is fluorinated to obtain the compound of formula (15); the compound of formula (15) is subjected to halogenation to obtain the compound of formula (16); and the compound of formula (16) is condensed with thymine base to obtain the compound of formula (17),



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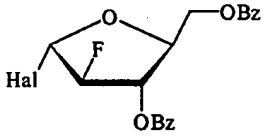
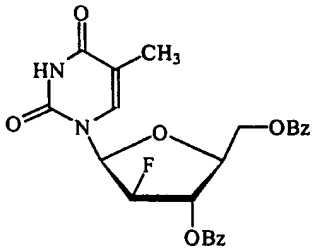


(16)



(17)

wherein Hal represents a halogen atom; and

g) the compound of formula (17) is treated with ammonia in methanol to produce the desired L-FMAU of formula (1).

3. The process as defined in claim 1, wherein the oxidation in reaction b) is carried out using aqueous chromic acid, sodium dichromate, pyridinium chlorochromate, pyridinium dichromate, potassium permanganate, lead tetraacetate/pyridine, oxygen over platinum/carbon catalyst, RuO_4, $RuO_4/NaIO_4$, dimethylsulfoxide/dicyclohexylcarbodiimide, a proton donor, silver carbonate, triphenyl bismuth carbonate, Oppenauer oxidation (aluminum alkoxides in acetone), chlorine dioxide, dimethylsulfoxide/oxalyl chloride, dimethylsulfoxide/sulfuryl chloride, dimethylsulfoxide/thionyl chloride, dimethylsulfoxide/toluenesulfonyl chloride, dimethylsulfoxide/trifluoroacetic anhydride or dimethylsulfoxide/acetic anhydride.

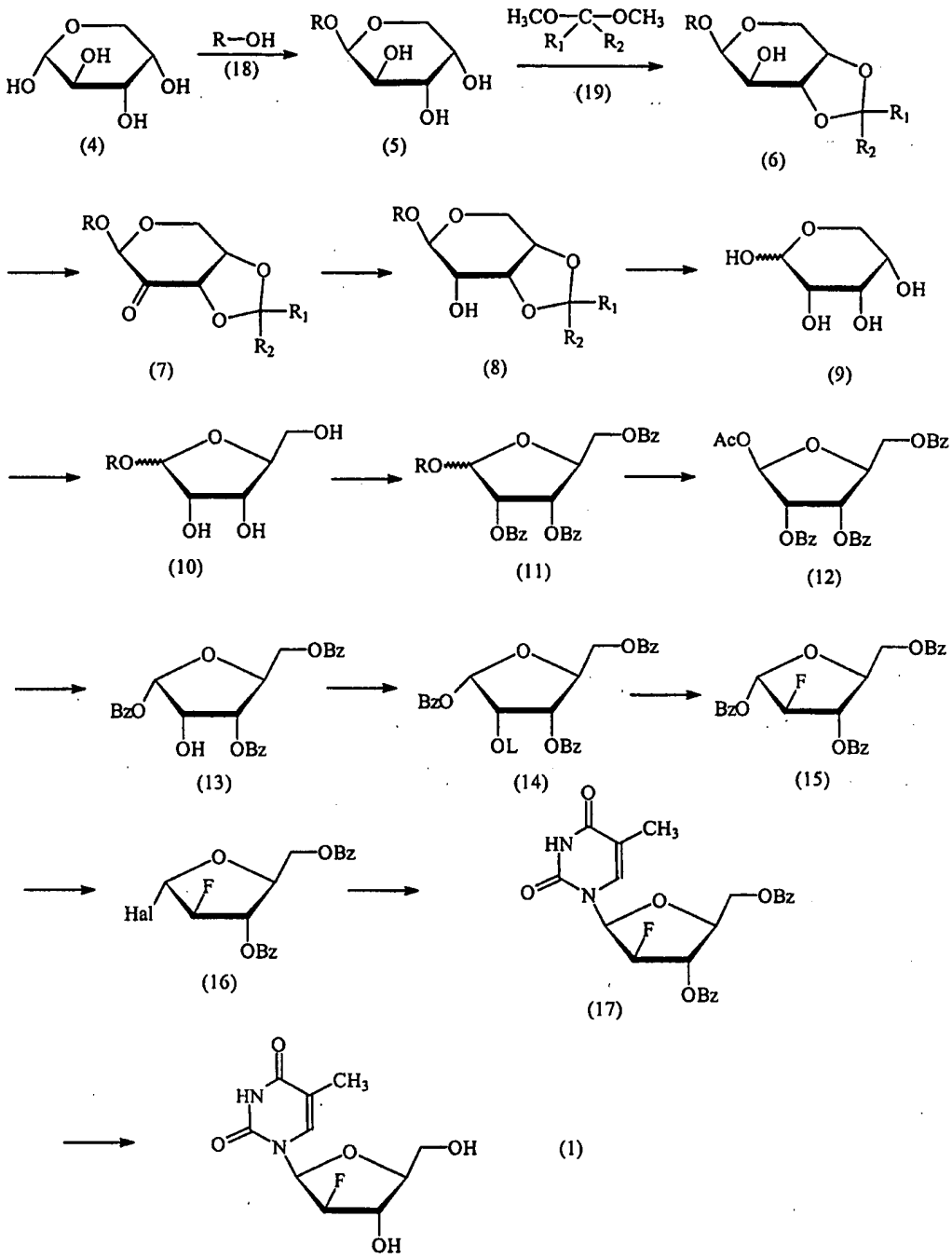
4. The process as defined in claim 1, wherein the reduction in reaction b) is carried out using sodium borohydride, diisobutylaluminum hydride, lithium borohydride, sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, potassium borohydride, Raney nickel, rhodium/hydrogen, palladium/hydrogen, platinum/hydrogen, rubidium/hydrogen or rubidium-silica/hydrogen.

5. The process as defined in claim 1, wherein in the reaction d) the reaction by-product 1-hydroxy-isomer is removed using diethyl ether or dibutyl ether.

6. The process as defined in claim 1, wherein the reaction e) is carried out using imidazole and sulfuryl chloride to introduce imidazolylsulfonyl group as a reactive leaving group.

7. The process as defined in claim 1, wherein the fluorination reaction in reaction f) is carried out using potassium hydrogen fluoride/hydrofluoric acid/pyridine or hydrofluoric acid/triethylamine.

Figure 1:



INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/IB 97/01254

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H19/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 20595 A (UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC.) 3 August 1995 cited in the application see figures 4,5,7 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 1998	04/03/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scott, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/IB 97/01254

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9520595 A	03-08-95	US 5587362 A	24-12-96
		AU 1737695 A	15-08-95
		BG 100792 A	31-03-97
		BR 9506596 A	09-09-97
		CN 1143966 A	26-02-97
		EP 0748330 A	18-12-96
		FI 962986 A	26-07-96
		HU 75514 A	28-05-97
		JP 9508394 T	26-08-97
		NO 963138 A	26-09-96
		SK 92696 A	06-08-97
		US 5565438 A	15-10-96
		US 5567688 A	22-10-96